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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,696	12/13/2000	Ernesto Freire	03940022BA	6797

30743 7590 06/03/2003

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

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DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/734,696

Applicant(s)

FREIRE ET AL.

Examiner

Marjorie A. Moran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 March 2003.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-4,6-10,13,15 and 17 is/are pending in the application.
- 4a) Of the above claim(s) 3,4,15 and 17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,6-10 and 13 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. All rejections and objections not reiterated below are hereby withdrawn.

Election/Restrictions

Claims 3-4, 15 and 17 are again withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 6.

This application contains claims 3-4, 15, and 17 drawn to an invention nonelected in Paper No. 6. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

Applicant is reminded that if applicant desires priority under 35 U.S.C. 119 (e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. For example, the phrase -- and claims benefit to Provisional US Application 60/066,495, filed 11/24/1997-- should be added to the end of the priority statement added in the amendment filed 12/13/00.

The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

The instant declaration claims priority to two Provisional Applications, but support for the instant claims is found in only one. Provisional Application 60/048,274 discloses a Figure 1 which shows most of the claimed method steps. However, the provisional's Figure 1 does not disclose a step of determining the three-dimensional coordinates of an energy minimized structure of a selected compound when that compound is bound to a binding site. 60/048,274 discloses various methods for designing an ideal ligand and predicting binding affinities, but other than in the Figures, does not disclose actual method steps for predicting a binding affinity. 60/048,274 does not disclose a method comprising a step of determining the three-dimensional coordinates of an energy minimized structure of a selected compound when that compound is

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bound to a binding site anywhere. Provisional application 60/066,495, filed 11/24/1997, provides support for the instantly claimed methods, specifically on page 13. For these reasons, priority is not granted to the filing date of 60/048,274. Priority for the instant claims is granted only to the filing date of Provisional Application 60/066,495, of 11/24/1997.

It is noted that applicant has amended the specification, in the response filed 3/7/03, to include a heading "CROSS-REFERENCE TO RELATED APPLICATION" but has not amended the specification to recite any related or priority application numbers.

Specification

The abstract of the disclosure is objected to because the first "sentence" is not complete. Appropriate correction is required. See MPEP § 608.01(b).

The proposed amendment to the abstract filed with the response of 3/7/03 would overcome this objection. It is noted that the proposed amendment has not been entered as a new (i.e. amended) abstract must be filed on a separate sheet of paper. See MPEP 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and/or use the invention. This is an ENABLEMENT rejection.

The factors to be considered in determining what constitutes undue experimentation were summarized by the board in *Ex parte Forman* (230 USPQ 546 (BdPatApp&Int 1986)) and affirmed by the court in *In re Wands* (8 USPQ2d 1400 (CAFC 1988)). These factors are the quantity of experimentation; the amount of direction or guidance presented in the specification; the presence or absence of working examples; the nature of the invention; the state of the prior art; the level of skill of those in the art; predictability or unpredictability of the art; and the breadth of the claims.

Methods wherein a Gibbs free energy of binding is determined for binding of an atom to an ideal ligand *for the atom* are not enabled as neither the specification nor the prior art teach how to determine what is an ideal ligand for an individual atom.

The instant specification defines an "ideal ligand", on page 11, as one which is perfectly complementary to the binding site of a target molecule (protein). The specification further teaches, on page 10, that binding affinity of (an idealized) ligand for a given binding site depends on "the chemical composition (atom **types**), size and topology of the binding site itself..." (emphasis added by examiner). Pages 10-21 of the specification disclose that an ideal ligand for a potential binding site is an aggregate or set of atoms obtained by global optimization of binding Gibbs energy. All of the definitions of the specification specifically state or certainly suggest that the binding site for which an ideal ligand is modeled comprises multiple atoms. Nowhere does the specification specifically disclose that an ideal ligand is modeled for an individual atom. The state of the art is such that how to calculate a Gibbs energy of binding between two atoms is known. However, it is also generally accepted in the art that binding sites on target molecules comprise at least multiple atoms, or multiple molecules (e.g. nucleic acids, amino acids). The state of the prior art is also such that how to calculate the binding energy of a ligand for a binding site comprising multiple atoms is known. See e.g. DELISI et al. (US 5,495,423). However, the prior art does not teach how to identify an ideal ligand for a single

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atom, and thus does not teach how to calculate a free energy (e.g. a Gibbs binding energy) between an individual atom and an ideal ligand for that atom. The specification provides guidance in the form of working examples for how to identify a binding target/site on a molecule, how to design an ideal ligand for an identified binding target comprising multiple atoms, and for how to calculate Gibbs energy of binding between atoms (pp. 44-45 and 54-58), but there are no working examples for how to determine what is an ideal ligand for an individual atom, whether that atom is in an identified binding site or not. The knowledge of skill in the art is acknowledged to be high. Despite this, and given the lack of guidance in either the prior art or the instant specification for how to determine what is an ideal ligand for an individual, lone atom, it would require undue experimentation for one skilled in the art to determine how to determine, for any atom in a molecule, a predicted Gibbs free energy of binding of the atom to "an ideal ligand for the atom." For the reasons set forth above, claims 2 and 13 are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 13 recite the phrase "an ideal ligand for the atom", each in step (a), part (ii). The specification does not define what is an "ideal ligand" for a single atom, as set forth above. One skilled in the art would therefore not know what the metes and bounds of an "ideal ligand" for "each atom in a molecule" is intended to be. For this reason, the claims are indefinite.

Claim Rejections - 35 USC § 102

Claims 2, 6, 8, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by DELISI et al. (US 5,495,423).

Applicants arguments filed 3/7/02 have been fully considered but are not persuasive. With respect to claims 2 and 13, applicant argues that as a "method of generating binding targets is deemed patentable, a method of predicting the binding affinity of a ligand for such a binding target should also be patentable." In response, it is noted that the method of claim 2 and the system of claim 13 recite inputting data for a binding site selected from a plurality of binding sites "generated by" particular steps. It is noted that neither the method nor the system/program claimed are limited to actually perform the steps for generating a plurality of binding sites. Further, the recited steps merely result in a prediction of binding targets. It is noted that the allowed claims of US 6,226,603 are directed to methods, not products. There is no indication that the products made by the allowed methods are patentable, or distinguishable from other products of the prior art. The steps of predicting a binding site do not structurally limit the binding site (or coordinates) for use in the method or system claimed. This is equivalent to a "product by process" limitation, wherein applicant is intending to limit the product (coordinates) used in the method by the method of prediction of binding sites. The MPEP 2113 states: "If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)." The instant claims do not recite any limitation with regard to the binding targets so predicted (i.e. the "products" for use in the method are not limited to any particular set of coordinates). As the steps for predicting a binding target do not limit the binding target to one which different from a binding site used in the method of DELISI, and DELSI teaches all of the

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method/program steps for determining the binding affinity of a ligand to a binding target of a molecule, the examiner maintains that DELISI anticipates claims 2 and 13.

With regard to claims 6 and 8, applicant argues that DELISI does not teach energy minimization using a dipeptide, but teaches energy minimization of one amino acid at a time. However, applicant also admits on page 7 of the response that the "peptide that is finally docked may be potentially of any length" and that "low energy conformations of the docked ligand are then chosen" for further processing. As DELISI clearly teaches that peptides for use in his method may be 2 to about 25 amino acids in length, DELISI's "peptide that is finally docked", as admitted by applicant, include dipeptides. If the peptide from which terminal anchor residue positions are energy-minimized is a dipeptide, then the calculation of lowest energy for binding is necessarily for the dipeptide. Applicant's arguments that the claimed method is based on use of "seed dipeptides" as opposed to known sequences (as in the method of DELISI) are moot as the claimed method does not recite any limitation of a dipeptide's origin. Applicant is reminded that the claims recite open claim language (comprising) and therefore do not exclude additional method steps which may be taught by the prior art. The examiner maintains that DELISI teaches all of the claimed method steps, and therefore maintains that claims 6 and 8 are anticipated.

Claim Rejections - 35 USC § 103

Claims 2, 6-10 and 13 are again rejected, as previously set forth in the office action of 11/7/02, under 35 U.S.C. 103(a) as being unpatentable over the combination of DELISI et al. (US 5,495,423) and SHAKHNOVICH et al. (US 5,854,992, filed 9/26/1996).

Applicants arguments filed 3/7/02 have been fully considered but are not persuasive. Applicant argues that claims 2 and 13, as amended, are allowable, and repeats that DELISIS

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does not teach dipeptides. As set forth above, the examiner maintains that DELISI teaches the claimed methods. Applicant further argues that the combination of DELISI and SHAKHNOVICH would not have been obvious, presumably because one would not have expected success in combining the teachings of DELISI and SHAKHNOVICH. Applicant asks if the H₂ molecule of SHAKHNOVICH be used instead of or in addition to the single amino acid molecule of DELISI? In response, it is noted that the previous office action did not state that it would have been obvious to have added an H₂ molecule to the peptide(s) of DELISI, but that the *concept* of adding to a growing energy minimized structure, as taught by SHAKHNOVICH, combined with the teaching of DELISI for adding amino acids to those already energy minimized, would have made performing energy minimizations on ever larger peptides obvious. It is again noted that the claims do not recite adding peptides to a *seed dipeptide*, but only recite polypeptides "including" the dipeptide of claim 6. If even one energy minimized terminal peptide in the method of DELISI is a dipeptide, then the energy minimization of the "filled in" peptides bound to a binding site in the method of DELISI encompasses the methods of claims 6-10. For these reasons, the examiner maintains that the combination of DELISI and SHAKHNOVICH makes obvious the claims, and maintains the rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3524.

mam
June 2, 2003

MARJORIE MORAN
PATENT EXAMINER

